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Prospective multicentre study using high intensity focused ultrasound (HIFU) for the focal treatment of prostate cancer: Safety outcomes and complications

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Abstract: Purpose To investigate focal therapy using High Intensity Focused Ultrasound (HIFU) for the treatment of localized prostate cancer (CaP), we analyzed the safety and complications of this procedure. Methods Patients (pts) eligible for this multicenter prospective cohort study suffered from low to intermediate risk localized CaP with no prior treatment. After tumor identification on multiparametric MRI and in prostate biopsy, the lesions were treated with HIFU observing a safety margin of 8 to 10 mm. Adverse events (AE) after 30 and 90 days, as well as the required interventions were assessed and stratified for treatment localizations. Results Of the 98 men included in the study in two European centers, 35 (35.7%) experienced AEs in the first 30 days after HIFU intervention with Clavien-Dindo grade II: 15 pts (15.3%) had a postoperative urinary tract infection and 26 pts (26.5%) a urinary retention. Four pts (4.1%) underwent subsequent intervention (Clavien-Dindo grade IIIa/b). The number of late postoperative complications occurring between 30 and 90 days after intervention was low (2.0%). The highest complication rate was associated with tumors located at the anterior base (50.0%). The inclusion of the urethra in the ablation zone led to AEs in 20 out of 41 cases (48.8%) and represented a significant risk factor for complications within 30 days (odds ratio = 2.53; 95% confidence interval: 1.08–5.96; P = 0.033). Conclusions Focal therapy of CaP lesions with a robotic HIFU-probe is safe and renders an acceptable rate of minor early AEs. The inclusion of the urethra in the ablation zone leads to an increase in early complications and should be avoided whenever possible.

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Prospective Multicentre Study using High Intensity Focused Ultrasound (HIFU) for the Focal Treatment of Prostate Cancer: Safety Outcomes and Complications

Original Research Article

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Abstract

Purpose: To investigate focal therapy using High Intensity Focused Ultrasound (HIFU) for the treatment of localized prostate cancer (PCa) we analyzed the safety and complications of this procedure.

Methods: Patients (pts) eligible for this multicenter prospective cohort study suffered from low to intermediate risk localized PCa with no prior treatment. After tumor identification on multiparametric MRI and in prostate biopsy, the lesions were treated with HIFU observing a safety margin of 8-10 mm. Adverse events (AE) after 30 and 90 days as well as the required interventions were assessed and stratified for treatment localizations.

Results: Of the 98 men included in the study in two European centers, 35 (35.7%) experienced AEs in the first 30 days after HIFU intervention with Clavien-Dindo grade ≤ II: 15 pts (15.3%) had a postoperative urinary tract infection and 26 pts (26.5%) a urinary retention. Four pts (4.1%) underwent subsequent intervention (Clavien-Dindo grade IIIa/b). The number of late postoperative complications occurring between 30 and 90 days after intervention was low (2.0%). The highest complication rate was associated with tumors located at the anterior base (50.0%). The inclusion of the urethra in the ablation zone led to AEs in 20 out of 41 cases (48.8%) and represented a significant risk factor for complications within 30 days (OR = 2.53; 95% CI: 1.08 to 5.96; p = 0.033).

Conclusions: Focal therapy of PCa lesions with a robotic HIFU-probe is safe and renders an acceptable rate of minor early AEs. The inclusion of the urethra in the ablation zone leads to an increase in early complications and should be avoided whenever possible.

Keywords: HIFU, focal therapy, localized prostate cancer, urethra sparing, minimal invasive, complication

Highlights

- HIFU for the treatment of localized prostate cancer is feasible and safe
- Most adverse effects are well manageable and major complications rare
- The inclusion of the urethra in the ablation zone must be avoided whenever possible
- Tumors treated at the anterior base provoke the highest complication rates

1. Introduction

The idea of treating the index lesion only is challenging current treatment dogmas in prostate cancer (PCa)[1]. To reduce overtreatment of low and intermediate risk tumors, an increasing focus on new treatment strategies is required [2,3]. These include focal therapies such as high intensity focused ultrasound (HIFU), which has been shown to produce promising results as an alternative to radical whole-gland therapy in selected patient cohorts [4-7]. Due to its acceptable oncological outcome, a lower morbidity as well as a better preservation of quality of life (QoL), HIFU represents an interesting treatment modality for an increasing number of men with PCa [8]. The focal treatment of lesions allows a substantial reduction of common side effects of whole gland treatment [9,10]. Furthermore, most adverse effects of focal therapies are well manageable and major complications are rare [11].

Focal HIFU therapy is currently being investigated as first-line therapy in low- to intermediate-risk cancer situations and as a strategy to postpone an antiandrogen therapy in elderly patients [12,13]. Complications after whole-gland therapy or hemiablation with HIFU are well studied, not only in a curative-intended but also in a salvage setting [14-17]. To extend this knowledge our study focuses on adverse effects of a true focal treatment with tumor locations stratified by quarters of the prostate. In this study, we present pooled data from two European tertiary care centers, analyzing safety and complications of focal HIFU procedures for treatment of localized low- to intermediate-risk PCa with a curative intent. We focus on the impact of specific ablation zones and the risk for complications and subsequently required interventions.

2. Materials and Methods

Patients treated with HIFU in a primary treatment setting for localized low- to intermediate-risk PCa in two European centers (Zurich, Switzerland and Magdeburg, Germany) between May 2014 and January 2018 were included in two prospective phase II trials and data was pooled for analysis.

Inclusion criteria were: age (≥45 years in Zurich or 18 – 75 years in Magdeburg); a histologically proven PCa on transrectal or transperineal biopsies (Gleason-Score of ≤4 + 3 = 7b was accepted in case of unilateral disease); clinical stage T1 or T2; serum PSA-values ≤15 ng/ml and a life expectancy of patient ≥ 10 years at time of inclusion. Exclusion criteria were: androgen suppression or hormone treatment for PCa within the last 12 months; evidence of metastatic or nodal disease on bone scan or cross-sectional imaging; transurethral resection of the prostate (TURP) for symptomatic lower urinary tract symptoms (LUTS) within the last 6 months and the inability to receive pelvic magnetic resonance imaging (MRI).

After identification of the tumors on multiparametric MRI, perineal or transrectal targeted and mapping (Zurich) or random (Magdeburg) biopsies of the prostate were performed. The MRI or biopsy data (BiopSee®, Medcom, Germany) were fused and transferred into the Focal One® (EDAP, France) working station using the provided software. Patients were then treated with focal HIFU observing a safety margin of 8-10 mm. Large prostate volumes (i.e. >100 cm^3) were no limitation in case of posterior tumor locations when applying true focal treatment to PCa lesions. A perioperative transurethral and/or suprapubic urinary catheter was inserted for 2 days (Magdeburg) or 7 days (Zurich). Follow-up visits in the outpatient clinic took place after 4 to 6 weeks and 3 months with assessment of PSA-values and questionnaires. During this systematic follow-up regimen, the 30- and 90-day complication rate and the interventions for adverse events (AE) were documented.

The Clavien-Dindo classification of surgical complications was used to categorize AEs. An acute urinary retention (UR) is the inability to urinate that necessitates a temporary indwelling urinary catheter and is defined as Clavien-Dindo grade I. UR following removal of the catheter within the first week after HIFU-intervention was not regarded as a complication, unless the

indwelling urinary catheter remained for more than 10 days postoperatively. A urinary tract infection (UTI) in any part of the urinary system (i.e. cystitis, urethritis, pyelonephritis or epididymoorchitis) that requires antibiotic treatment (in addition to perioperative antibiotic prophylaxis) is defined as Clavien-Dindo grade II. Surgical interventions in local anesthesia (i.e. placement of suprapubic catheter) or general anesthesia (i.e. TURP) are regarded as Clavien-Dindo grade IIIa and IIIb, respectively. Gastrointestinal side effects (i.e. diarrhea, rectum injuries, fistulas or bleeding) were specifically registered during follow-up visits, as well as general complications according to Clavien-Dindo classification (i.e. deep vein thrombosis, pulmonary or cerebral embolism and other). We analyzed prostate and tumor size, tumor locations and HIFU treatment zones according to the documentation provided by the Focal One® device software. The lesions and the applied treatment zones were then assigned to halves and quarters of the prostate.

The primary endpoint of this study was any AE stratified for localization of the HIFU ablation zone. The secondary endpoints were the size and location of the treated tumor within the prostate, stratified for complications and subsequent interventions.

The data were analyzed with a Student's t-test and a univariate logistic regression for the comparison of the means; statistical significance was set at $p < 0.05$ (SPSS Statistics 25).

The studies were registered on ClinicalTrials.gov (NCT02265159) and the German Clinical Trials Register (DRKS00007775). Perioperative management and inclusion criteria may show slight deviations between the two centers.

3. Results

3.1. Baseline characteristics

A total of 98 patients were analyzed in the presented interim analysis. The median body-mass-index (BMI) was 25.9 kg/m^2 (20.5 – 35.3 kg/m^2). The last median PSA-value before HIFU-treatment was 6.5 ng/ml (1.03 – 14.9 ng/ml) and clinical T-stage was ≤2 with cT1 in 76.5% (n = 75), cT2 in 23.5% (n = 23). The Gleason-Score was 3+3=6 in 17.3% of patients (n = 17), 3+4=7a in 65.4% (n = 64) and 4+3=7b in 17.3% (n = 17). Median prostate volume in our cohort was 39.6 cm^3 (21.6 – 135.2 cm^3), whereas the treated tumor (index lesion) presented a median volume of 10.5 cm^3 (3.9 – 28.2 cm^3). See *Table 1* for baseline characteristics of our cohort.

3.2. Logistic regression analysis: Urethra inclusion, treated tumor volume, prostate size and body-mass index (BMI)

The inclusion of the urethra in the HIFU ablation zone led to AEs in 20 out of 41 cases (48.8%) and the logistic regression analysis showed a significantly higher risk for postoperative complication if the urethra was included (OR = 2.53; 95% CI: 1.08 to 5.96; p = 0.033). In contrast, a urethra-sparing ablation led to a lowered risk for postoperative complications with only 26.3% AEs (15 out of 57 patients, OR= 0.40; 95% CI: 0.17 to 0.93; p = 0.033). Furthermore, the risk for complications did not increase with higher tumor volumes treated (OR = 1.09, 95% CI: 0.99 to 1.20; p = 0.083). Neither prostate size (OR = 1.01; 95% CI: 0.99 – 1.03; p = 0.211) nor BMI (OR = 1.01; CI: 0.88 – 1.15; p = 0.874) were risk factors for a postoperative AE in our cohort.

3.3. Tumor locations

Unifocal and multifocal ablations were performed in 86 (87.8%) and 12 (12.2%) patients, respectively. The lesions were located as follows: right lobe 37.3 % (n = 28), left lobe 34.7% (n = 26), both sides 28.0% (n = 21). In total, 41.8% of all treatments (n = 41) included the urethra. Analyzing the prostate halves, posterior lesions were found in 72.4% (71 out of 98 patients), anterior lesions in 17.3% (17 out of 98 patients) of all cases. Apex tumors were present in 53.1% (52 out of 98 patients) and basal tumors in 35.7% (35 out of 98 patients). Patients who had a tumor either affecting a whole prostate lobe (n = 7) or stretched from apex to base (n = 8) could not be classified and are referred to as “overlapping”.

Furthermore, the subdivision of the prostate into quarters showed that most cancers were located either at the posterior apex (42.9%, 42 out of 98 patients) or at the posterior base (22.4%, 22 out of 98 patients). Tumor locations at the anterior apex (8.2%, 8 out of 98 patients) and the anterior base (8.2%, 8 out of 98 patients) were less common. Tumors that fully stretched either from posterior to anterior or from apex to base were classified as “overlapping” (n = 15). See *figure 1* for illustration.

3.4. Complications overall

In total 63 patients (64.2%) had no postoperative complication during the first 30 days after the intervention (early postoperative phase). Complications rated stage ≤ II according to Clavien-Dindo classification were noted in 35 cases (35.7%) within the first postoperative month: 15 patients (15.3%) had a postoperative urinary tract infection (UTI), 26 (26.5%) had a urinary retention (UR) and six patients (6.1%) had both complications (UTI and UR). Patients with UTI received additional antibiotic treatment and 20 out of 26 patients with URs had to be re-catheterized. Of the remaining six already catheterized patients, two (2.0%) had to be re-catheterized (Clavien-Dindo grade IIIa). Only two patients (2.0%) underwent TURP for recurrent UR caused by tissue sloughing following HIFU-treatment (Clavien-Dindo grade IIIb).

The incidence of complications between postoperative days 30 and 90 was low, with only one patient developing an UTI and one patient suffering from UR (total 2.0%). The treatments administered were the same as described above. The remaining 98.0% (n = 96) of all patients had no complications during the second postoperative interval.

3.5. Complications depending on tumor location

Subdividing the prostate halves into quarters, the treatments in the anterior base of the prostate turned out to result in the highest complication rate of 50.0% (4 out of 8 patients). By comparison, the ablation sites in the posterior base of the prostate provoked fewer complications (31.8%; 7 out of 22 patients). The probability of an AE following HIFU in the posterior apex was higher (35.7%, 15 out of 42 patients) than in the anterior apex (12.5%, 1 out of 8 patients). *See Table 2*. Due to the descriptive nature of our study and the rather small sample size in each of these subgroups, no statistical analysis was performed.

4. Discussion

Our study shows that the true focal therapy of PCa using fusion technology and a robotic HIFU-probe is a safe procedure and leads to an acceptable rate of early, mostly minor postoperative complications in appropriately selected patients. Almost two-thirds (64.2%) of our patients treated with HIFU experienced no AEs at all. However, we found evidence for an increased risk for early AEs after treatments involving the urethra (OR = 2.53; p = 0.033). The analysis by quarters of the prostate indicated a higher complication rate when treating tumors at the anterior base (50%).

The distance between the HIFU-probe and the index lesion is a crucial factor for subsequent complications, because longer distances result in more tissue involvement (i.e. tumors located at the anterior base). Therefore, we hypothesize that a larger distance to the treated area with consequent swelling, tissue necrosis and fibrosis leads to a higher rate of early complications. Furthermore, anterior lesions tend to affect the urethra due to the given distance and angle. As the urethra is the only organ structure assuring passage within the prostate, a damaged urothelium becomes susceptible for obstructions or ascending infections. A recent publication investigated the incidence, severity and timing of onset of complications after HIFU treatment in patients with PCa [18]. However, to the best of our knowledge, we are the first group to present a descriptive association between specific ablation zones and their complication rates.

Over the past years, different forms of focal therapies emerged as alternatives to radical whole-gland therapy in patients with low- to intermediate-risk PCa [19,20]. The change from radical options to organ-sparing treatment approaches is aimed at reducing overtreatment and adverse genitourinary side effects as well as ameliorating overall QoL [10]. HIFU is well accepted and ranks among the established focal treatment technologies, most of which are still considered experimental [4,19]. Nevertheless, patient selection for focal therapies should be based on prostate volume, risk classification, tumor size, location and multifocality [19,21,22]. The importance of a mandatory diagnostic multiparametric MRI with fusion prostate biopsies (plus

template) before allocating patients to HIFU treatment was underlined by various investigations [21,23].

Overall, patients treated with HIFU for localized PCa experience a rather low rate of postoperative complications and maintain a better QoL than patients after radical treatment options. Blana et al. demonstrated low numbers of postoperative complications (<10% altogether), while long-term efficacy with disease-free survival rates were 66% and 59% after 5 and 7 years, respectively [24]. A high number of men with satisfactory erections, good continence, early but self-resolving LUTS and a good QoL were also reported by Ahmed et al. [25]. Another study stated a lower rate of erectile dysfunction (ED) and urinary incontinence compared to robot-assisted laparoscopic radical prostatectomy (RARP) or external beam radiation [26]. A comparative analysis has looked into oncological and functional outcomes of partial gland ablation (PGA) vs. RARP and showed that PGA renders better preservation of continence and potency after a mean follow-up of 38 months. However, these improved outcomes came at the cost of a higher rate of treatment failures and the need for salvage therapy after PGA [27].

With the increasing experience of urologists and the technological advances in the field of HIFU ablation, the overall treatment volumes were decreasing considerably. Initially, whole-gland ablation (WGA) was investigated on patient cohorts with long follow-up intervals [28,29]. Crouzet et al. analyzed more than 1000 patients treated with WGA for localized PCa: Next to rather low rates of UTIs (3.9%) or URs (7.6%), they additionally reported on significant numbers of stress urinary incontinence (SUI, 18.7% grade I and 5% grade II), bladder outlet obstructions (BOO, 16.6%), hematuria and tissue sloughing (5.5%) and late complications such as urethral stenosis (9%) or fistulas (0.4%). Yet, in a study by Dickinson et al., a remarkable 227 out of 754 patients (30%) had to undergo endoscopic intervention for LUTS after WGA and the rate of patients with pad-free status decreased from 87% pre- to 56% post-HIFU. This supports our hypothesis of an increased rate of adverse effects with higher volumes of tissue ablation. Two studies investigated cohorts treated for unilateral, organ-confined PCa

by hemiablation and reported on complication rates. Feijoo et al. indicated minor adverse effects on genitourinary function with a low complication rate of only 14% (Clavien-Dindo grade I-III) after a median follow-up of 12 months in 67 patients [30]. No decrease in QoL was observed 12 months after HIFU hemiablation in a prospective multicenter trial in France: In this cohort of 111 patients, a low morbidity with preserved continence and erectile function (97% and 78%, respectively) but a high rate of Clavien-Dindo grade III complications (13%) was observed [15]. In comparison to our results, hemiablation tends to provoke a higher rate of Clavien-Dindo grade III complications.

The final stage in the development of the HIFU treatment spectrum is the true focal approach – therefore, the comparison of our results with trials performing partial gland ablation (PGA) is of interest as well. Bass and colleagues recently published their results on HIFU therapy with PGA in localized prostate cancer as definitive treatment approach [31]: They included 150 patients with 166 procedures and reported a complication rate of 33% (mostly Clavien-Dindo grade I or II). This rate is well comparable to our published complication rate (35.7% overall). However, they reported on eight individuals requiring subsequent surgical intervention or developing urethro-rectal fistula (four patients each). In contrast, we have not witnessed any rectal complications in our cohort. One must be aware of the fact that treatment success and overall complications vary among centers of expertise. A systematic review of 13 studies with 543 included patients treated with PGA in the primary (11 studies) and salvage setting (two studies) demonstrated a marked heterogeneity in outcomes. Altogether, they reported a complication rate of up to approximately 50% (mostly Clavien-Dindo grade I or II), which is substantially higher than in our presented cohort, including the presence of urethral strictures and SUI [12].

We are convinced that urethra-sparing focal HIFU treatment may prevent early and late postoperative complications. Shoji et al. investigated the role of urethra-sparing HIFU treatment compared to WGA and found several significant differences with regard to functional outcomes (IPSS-Score) [16]. They concluded that the urethra-sparing approach and the

avoidance of anterior lesions has the potential of preventing urethral strictures and BOOs. Our results support these findings by showing a protective effect of urethra-sparing HIFU ablation: Only 26.3% (lower than average) of our patients developed AEs after urethra-sparing treatment (OR= 0.40), whereas an inclusion of the urethra in the ablation zone led to complications in 41.8% (higher than average) of our patients (OR = 2.53).

Among the limitations of our study is the rather small sample size in the subgroups. In addition, patients need to pay for parts of the HIFU treatments in Switzerland, since it is still considered an experimental treatment approach. This may lead to a patient selection bias. Although focal HIFU therapy is an emerging technique, bigger cohorts with long-term follow up data are needed to better answer questions on specific complications according to treatment areas combined with the results on oncologic efficacy.

5. Conclusion

True focal HIFU ablation is a safe and feasible therapy in selected patients with low- to intermediate-risk PCa. The analysis of our pooled data from two prospective Phase II trials showed that most of the complications after HIFU treatment occur during the first 30 days after the intervention. The vast majority of complications in our study were low grade according to Clavien-Dindo classification (≤ II) and only four patients required subsequent surgical intervention (TURP or insertion of suprapubic indwelling urinary catheter). The highest rate of complications was recorded after treatment of tumors in the anterior base of the prostate. A distinct risk factor for complications was the inclusion of the urethra in the ablation zone. Therefore, we suggest focal HIFU treatment only for patients not requiring the inclusion of the urethra.

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Legends to illustrations

- *Table 1:* Baseline characteristics of patients included in the cohort.

  Abbreviations: PSA = prostate specific antigen, HIFU: High intensity focused ultrasound.
- *Table 2:* Treatment locations and their complications by quarters of the prostate in the first 30 days postoperatively. Overlapping: Tumor lesion involving more than one quarter or not attributable to a single quarter.
- *Figure 1:* Areas of tumor involvement. Overlapping areas not displayed. Unifocal: Single lesion identified. Multifocal: >1 lesion identified.

		N (%)	
Total number of patients		98 (100)	
Magdeburg		18 (18.4)	
Zurich		80 (81.6)	
		Median (+/-Std.)	**Range**
Age (years)		66 (7.0)	50 - 78
Body Mass Index (kg/m2)		25.9 (3.2)	20.5 - 35.3
Last PSA value before HIFU (ng/ml)		6.5 (2.8)	1.03 - 14.9
Prostate volume (cm3)		39.6 (20.7)	21.6 - 135.2
Treated tumor volume (cm3)		10.5 (5.0)	3.9 - 28.2
	Subgroup	**N (%)**	
Clinical T-Stage	cT1	75 (76.5)	
	cT2	23 (23.5)	
Gleason-Score	3+3=6	17 (17.3%)	
	3+4=7a	64 (65.4%)	
	4+3=7b	17 (17.3%)	

Table 1: Baseline characteristics of patients included in the cohort.

Abbreviations: PSA = prostate specific antigen, HIFU: High intensity focused ultrasound.

Location	Patients (n)	Percent (%)	Any Complication (n)	Percent (%)
posterior apex	42	**42.9**	15	35.7
posterior base	22	22.4	7	31.8
anterior apex	8	8.2	1	12.5
anterior base	8	8.2	4	**50.0**
overlapping	15	7.7	6	40.0
missing	3	3.1	2	66.7
total	98	100	35	35.7
inclusion urethra	41	41.8	20	**48.8**

Location	Specific Complications Urinary Tract Infection (n)	Percent (%)	Urinary Retention (n)	Percent (%)
posterior apex	5	11.9	12	**28.6**
posterior base	4	18.2	4	18.2
anterior apex	1	12.5	1	12.5
anterior base	3	**37.5**	1	12.5
overlapping	2	13.3	5	33.4
missing	1	33.4	1	33.4
total	15	15.3	23	23.5

Table 2: Treatment locations and their complications by quarters of the prostate in the first 30 days postoperatively. Overlapping: Tumor lesion involving more than one quarter or not attributable to a single quarter.

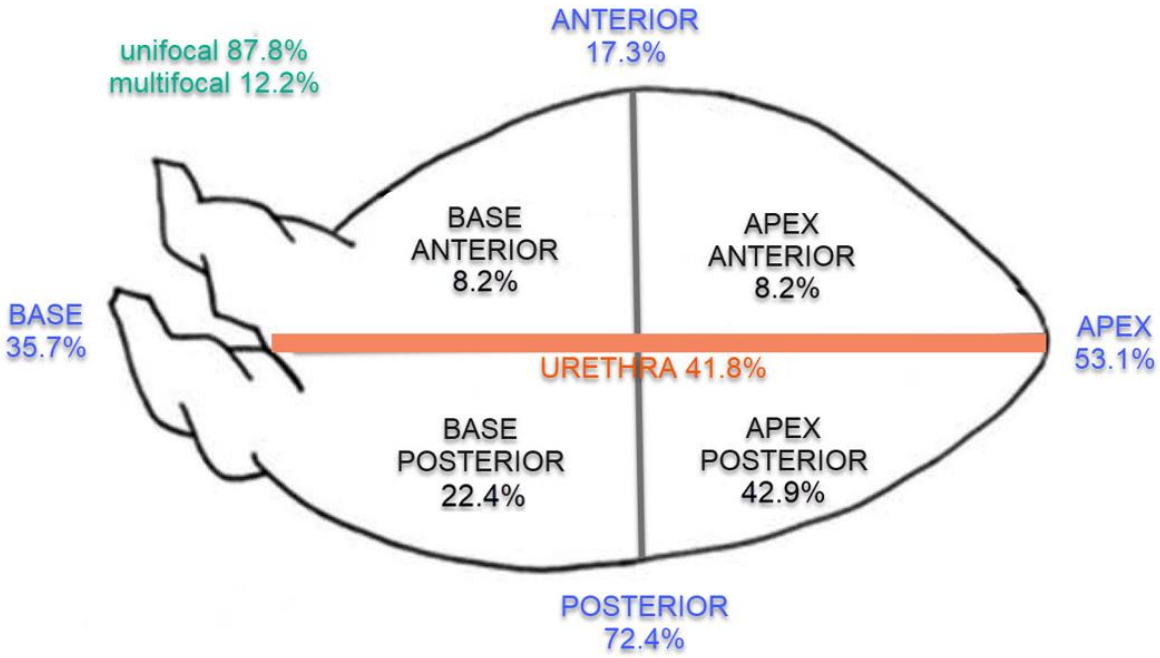

Figure 1: Areas of tumor involvement. Overlapping areas not displayed. Unifocal: Single lesion identified. Multifocal: >1 lesion identified.